REMARKS

I. Support for the Amendments

Claims 1, 24-25, 30-31, and 37 have been amended, and new claims 48-49 have been added, as shown in the following listing of claims, which will replace all prior versions and listings of claims in the application.

Support for claims 1, 24-25, 30-31, and 37 as amended and for new claims 48-49 can be found in the original specification, e.g., from pages 2-5, in the Examples and in the original and amended claims. Detailed support for amended claims 1, 24-25, 30-31, and 37 and new claims 48-49 can be found on pages 2-4, 5, and 6-7 of the specification, particularly in the carry-over paragraph on pages 2-3 and in claim 2 (now canceled), as well as in the middle paragraph on page 5.

II. Status of the Claims

Claims 1, 3-35, and 37-47 were previously pending in the present application. In the Office Action, mailed 26 July 2004, the Examiner rejected claims 1, 3-26, 28-33, 37-42, 45, and 46 and objected to claims 27, 34, 35, 43, 44, and 47.

Currently, claims 1, 3-35, and 37-49 are pending in the application, with claims 1, 13, 14, 24, 25, 30, 31, 34, 35, and 37 being the independent claims. Claims 48-49 are new claims.

III. A Supplemental Declaration and Power of Attorney is Enclosed Herewith in Compliance with 37 C.F.R. 1.63(c)

The Examiner has acknowledged papers filed under 35 U.S.C. §119 (a)-(d) on an application filed in the United Kingdom on 17 November 1998. On 17 May 2001, the present application was filed under 35 U.S.C. §371, along with a Declaration and Power of Attorney bearing the signatures of both joint inventors. The Examiner has requested a supplemental oath or declaration listing this application and in compliance with 37 C.F.R. §1.63(c).

Applicants thank the Examiner for acknowledging the priority claim. A Supplemental Declaration and Power of Attorney is enclosed herewith as signed by inventor Dr. Neil James Butt. As noted in an earlier telephone conversation with the Examiner, Applicants are currently endeavoring to obtain the signature of Dr. Christopher Peter Jones. The Examiner is invited to telephone Applicants' undersigned representative if it will assist in any way.

IV. Rejection of Claims 1, 3-12, 15-23, and 37-40 under 35 U.S.C. § 112, Second Paragraph, Is Traversed, but Partially Accommodated

The Examiner has rejected claims 1, 3-12, 15-23, and 37-40 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. In particular, the Patent Office alleges:

> Claims 1 and 37 are vague and indefinite in that the metes and bounds of the word "substantially" are unclear. The term "substantial" is a relative one not defined by the claim, no single set of conditions is recognized by the art as being "substantial" and because the specification does not provide a standard for ascertaining the requisite degree. [P. 3.]

Applicants respectfully traverse this rejection. In the interests of furthering prosecution in a timely manner, Applicants have amended claims 1 and 37, but have retained the language in new claims 48 and 49 and request reconsideration of this rejection accordingly.

First, the term "substantially" in the claims should not necessarily result in a rejection under 35 U.S.C. §112. The Patent Office cites In re Giolito and Hoffman ("It is immaterial whether similar claims have been allowed to others"), maintaining that "each application is reviewed on its own merits." Applicants respectfully advance this argument as evidence of the general standard of practice in the Patent Office, rather than as an argument for *stare decisis*.

The Patent Office further alleges:

> It is not disputed that the word "substantially" has a definition nor that the specification provides guidance for the evaluation of DNA concentrations in the particular phases. Rather, the term "substantial" is a relative and no single set of conditions is recognized by the art as being "substantial". Establishing "substantial" amounts of DNA in a given phase that amount that will satisfy the limitation of the claim that it be "substantial" is open to interpretation by the practitioner. [P. 4.]

Applicants respectfully submit that claim language is not required to be limited only to a single set of conditions. Rather, (1) the term can be defined (e.g., as in the dictionary meaning[1]) and (2) the specification provides examples and a method by which the skilled practitioner can determine any additional conditions without undue experimentation (e.g., Example 1, especially Table of Extraction Mixtures Tested (pp. 6-7)).

The Table of Extraction Mixtures Tested (pages 6-7) describes the Plasmid DNA Recovery as No, Poor, OK, or Good. "Good" is defined as "Approximately 1 μg DNA recovery"; "OK" is defined as "Approximately 200 ng DNA recovery"; and "Poor" is defined as "Just visible on agarose gel electrophoresis." Clearly, some separation conditions are better than others. Those that are "OK," for example, have only some plasmid recovery. Therefore, it appears that, while these conditions are "OK" and, therefore, may be of some use, they do not result in an absolute sequestration of the plasmid DNA in the organic (e.g.,

[1] Webster's New Collegiate Dictionary (1990), copy provided with Amendment mailed April 15, 2004.

butanol) phase. Rather, it may be that a larger percentage of the plasmid DNA in these samples is remaining in the aqueous phase with the genomic DNA. An "OK" plasmid recovery may be acceptable in some circumstances (i.e., only 20% of the amount of DNA from a "Good" recovery).

Moreover, it is well-known to those of ordinary skill in the art that the difference between plasmid DNA and genomic DNA is readily observable on an agarose gel electrophoresis, due to the generally different sizes, conformations, and charges and, therefore, migration rates of the two types of DNA. The results of an agarose gel electrophoresis, which not involve undue experimentation, would enable the practitioner of the present invention to observe whether the plasmid DNA was "substantially" in one fraction, while the genomic DNA was "substantially" in the other fraction.

In the interests of furthering prosecution in a timely manner, Applicants have amended claims 1 and 37, but have retained the language in new claims 48 and 49 and request reconsideration of this rejection accordingly.

Regardless, Applicants wish to make it clear on the record that the partitioning of plasmid DNA and/or genomic DNA need not be 100% in order to fall within the limitations of the present claims.

For these reasons, Applicants respectfully traverse the Examiner's rejection of claims 1, 3-12, 15-23, and 37-40 under 35 U.S.C. § 112, second paragraph, and assert that claims 1, 3-12, 15-23, and 37-40 are in a condition for allowance.

Therefore, Applicants request reconsideration and withdrawal of the rejections made under 35 U.S.C. §112, second paragraph.

VI. Rejection of Claims 1, 3-7, 9-23, 25-26, 37-40, and 45-46 Under 35 U.S.C. §112, First Paragraph, Is Traversed

The Examiner has rejected claims 1, 3-7, 9-23, 25-26, 37-40, and 45-46 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Examiner has stated that this is a new rejection. The Patent Office alleges that the claims contain subject matter, which is not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

In particular, the Patent Office alleges:

> Applicants claim a method for isolating plasmid DNA from genomic DNA "under conditions to denature genomic DNA". Specifically, applicants claim use of a genus of basic conditions and bases to denture the DNA.
> Applicants claim a genus of precipitating agents comprising alcohol.
> ****
> Applicants teach that the instantly claimed invention distinguishes itself from the prior art by minimizing steps required for the isolation of plasmid DNA from genomic DNA by the exploitation of the differential solubility between the two types of DNA under denaturing conditions. Following denaturation, in the presence of an extraction mixture comprised of chaotrope, butanol and water, genomic DNA separates into aqueous phases and plasmid DNA into butanol phase. Therefore, as an essential element, the invention claims a "condition" in which genomic DNA is denatured and can be retained in the aqueous phase of the extraction mixture while the plasmid DNA selectively migrates into the butanol phase. In the instant specification, we are only taught that appropriate conditions for denaturation are high temperature of 65°C or higher for several minutes or basic conditions in which base is present. The disclosure of the afore stated conditions is not accompanied by a disclosure as to the relative properties of the condition that denatures DNA for retention in aqueous phases and yet allows plasmid DNA to migrate into the butanol phase. Therefore, there is no actual reduction to practice or clear description of what is required for "conditions to denture genomic DNA" to meet the limitations of the instant invention. Given the diversity of conditions that denature DNA and the inability to determine which will also meet the limitations of the instant invention, it is concluded that the invention must be empirically determined. In an unpredictable art, the disclosure of two species would not represent to the skilled artisan a representative number of species sufficient to show applicants were in possession of claimed genus.

> Furthermore, while applicants claim a genus of basic conditions, and a genus of bases to be used to denature the DNA, applicants only teach use of NaOH. Specifically, sodium hydroxide at concentrations of 90 mM to 200 mM is shown to be adequate for "good" plasmid recovery (page 6-7, table). There is no actual reduction to practice or clear description of what is required to denature genomic DNA to meet the limitations of the instant invention. For example, it is known that water can act as a weak base. Is this adequate as a component of the extraction mixture? Given the diversity of bases and the inability to determine which will also meet the limitations of the instant invention, it is concluded that the invention must be empirically determined. In an unpredictable art, the disclosure of one species would not represent to the skilled artisan a representative number of species sufficient to show applicants were in possession of claimed genus.
>
> Applicants teach that a precipitating agent such as alcohol can be used in the recovery step of the instant invention. The use of any alcohol as a precipitating agent is not disclosed in the prior art or the specification. Rather, the specification teaches the use of ethanol as a precipitating agent. Applicants have not reduced to practice or clearly described in pictures or descriptions the species of alcohols that would function as ethanol does precipitate the DNA. Applicants have not provided relevant identifying characteristics of ethanol such that nay alcohol could be used as a precipitating agent. Given the unpredictability of the art and the inability to determine what type of alcohol will precipitate DNA versus for example function in extraction mix, it is concluded that the invention must be empirically determined. In an unpredictable art, the disclosure of one species would not represent to the skilled artisan a representative number of species sufficient to show applicants were in possession of claimed genus. [Pp. 5-7.]

Moreover, in response to the previous arguments advanced by Applicants, the Patent Office further alleges:

> ****Applicants argue in their response essentially that pages 2-3 of the specification teaches a wide range of conditions for the denaturation of genomic DNA and that other conditions for denaturing DNA are well known in the art. Furthermore, applicants argue that they need not be limited to those conditions for which working examples have been provided. Finally, applicants state that the unpredictable art of denaturing conditions is unclear.
>
> The arguments filed 4/19/03 in response to similar grounds of rejection have been considered but are not persuasive. The specification teaches that the DNA material is mixed with reagents to denature the genomic DNA whereby the plasmid DNA is partitioned into an organic phase and the genomic DNA is partitioned into the aqueous phase (bridging paragraph page 2-3). Therefore, it is not enough to just denature the DNA. Rather differential solubility of plasmid and genomic DNA under denaturing conditions is an essential element required of the denaturing conditions. The specification teaches denaturation by elevated

> temperatures at 65°C or greater or addition of base preferably sodium hydroxide (page 3, line 2-16). This disclosure does not constitute written description for the identification of any condition required to denature the DNA such that the plasmid DNA migrates into the organic phase and the genomic DNA into the aqueous. Adequate written description requires more than a mere statement that the condition is part of the invention and a reference to a potential means of finding this condition. As to the unpredictable nature of the art, it is the identification of conditions in which the DNAs are partitioned into their respective phases that is unpredictable. Taken in total, the rejection states "(g)iven the diversity of conditions that denature DNA and the inability to determine which will also meet the limitations of the instant invention", the art can be considered to be unpredictable. [Pp. 7-8.]

Applicants respectfully disagree.

First, Applicants wish to clarify a statement made by the Patent Office ("Finally, applicants state that the unpredictable art of denaturing conditions is unclear."). Rather, Applicants are unclear as to why the Patent Office considers the denaturation of DNA to be an "unpredictable art," given "the diversity of conditions that denature DNA." Conditions for denaturing DNA have been well known to those of skill in the art for many years (see, e.g., Sambrook et al., Molecular Cloning: A Laboratory Manual (2d ed.), Cold Spring Harbor Laboratory Press, 1989[2]) and have been used in a variety of applications, such as in dideoxy sequencing, library screening, Southern blotting, and PCR. Long before the filing date of the present application, the concept of a melting temperature (T_m) of DNA had been explored and it was well established in the art that one of skill in the art could denature DNA by adjusting the temperature or the pH of the solvent, as well as by altering the identities and concentrations of ions in solution.[3]

With respect to the denaturation followed by precipitation, once denaturation of the genomic DNA has occurred, partitioning of the plasmid and genomic DNA is inevitable. The invention is characterized by the finding that plasmid and genomic DNA partition differently

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[2] *See also*, Voet & Voet, Biochemistry, John Wiley & Sons, 1989 (e.g., pp. 805-806, 815-816, and 844); Old & Primrose, Principles of Gene Manipulation: An Introduction to Genetic Engineering (4th ed.), Blackwell Scientific Publications, 1989 (e.g., p. 7); Watson et al., Molecular Biology of the Gene (4th ed.), Benjamin/Cummings Publishing Co., 1987 (e.g., pp. 243-244).

[3] *Id. See also* Sambrook et al., 1989.

in particular aqueous/organic solvent mixtures, and the claims should be similarly generic. To narrow the claims with respect to the precipitation agent would unduly restrict the scope of the claims.

The claims clearly define the method of the invention, because the precipitation of genomic DNA would be detectable by the skilled person when carrying out the method. A wide variety of precipitating agents could be employed to precipitate the plasmid DNA from the butanol and the skilled person would readily be able to recognize suitable agents or at the very least be able to identify such agents readily through routine experimentation. While water is a weak base, certainly the skilled person would not consider water alone (absent, e.g., heat or another denaturing factor) to be a suitable base for achieving denaturation of genomic DNA.

Applicants respectfully note that claims 25-26 and 45-46 are directed to an extraction mixture, rather than a method and traverse the rejection as it is applied to them.

Independent claim 1 currently amended, reads as follow:

> 1 (currently amended). A method for isolating plasmid DNA from genomic DNA in a DNA containing material which comprises plasmid DNA and genomic DNA, comprising the steps of:
>
> (i) extracting the plasmid DNA into butanol by mixing the material with butanol, a chaotrope, and water under conditions to denature the genomic DNA and forming an aqueous phase and a butanol phase,
>
> (a) wherein the genomic DNA is in the aqueous phase and the plasmid DNA is in the butanol phase, such that most of the plasmid DNA is isolated from the genomic DNA; and
>
> (b) wherein the conditions to denature the genomic DNA comprise basic conditions or a temperature of at least 65°C; and
>
> (ii) recovering the plasmid DNA from the butanol phase.

The other independent claims cited by the Examiner, claims 13, 14, and 37 also comprise a final step directed to "recovering the plasmid DNA from the butanol phase."

Dependent claims 15, 17, and 18 read as follows:

> 15 (previously presented). The method of claim 1, wherein the recovery step (ii) comprises mixing the butanol phase, which comprises plasmid DNA, with a precipitating agent that can precipitate the plasmid DNA from the butanol, and separating the precipitated plasmid DNA from the butanol.
>
> ****
>
> 17 (original). The method of claim 15 or claim 16, wherein the precipitating agent comprises an alcohol.
>
> 18 (original). The method of claim 17, wherein the alcohol is ethanol.

In essence, claim 15 comprises precipitating the plasmid DNA from the butanol using "a precipitating agent." In claim 17, the precipitating agent comprises an alcohol, and in claim 18, the alcohol is ethanol.

The specification provides the following:

> **In one arrangement**, recovery step (iii) includes precipitation of the plasmid DNA from the organic solvent. For example, the DNA-containing organic phase may be mixed with a precipitating agent that can precipitate the plasmid DNA from the organic solvent and the precipitated plasmid DNA is separated from the solvent. The precipitated plasmid DNA may also be washed in a washing step. The precipitating agent may comprises an alcohol such as ethanol and may further comprise an acetate salt such as sodium acetate. [Pp. 4-5; emphasis added.]

In addition, the Examples describe precipitation with ethanol and sodium acetate. Applicants respectfully submit that claim 18 is supported by this disclosure.

Conditions (basic, alcoholic) for precipitating DNA from organic solvents, such as alcohol, were well-known at the priority date (see, e.g., Sambrook et al., 1989). For example, it was well-known in the art long before the application was filed that DNA could be precipitated with isopropanol, in addition to ethanol (see, e.g., Sambrook et al., 1989). Once

denaturation is achieved, partitioning of the genomic and plasmid DNA requires no additional consideration or special conditions (see, e.g., the Examples).

The Patent Office explicitly objects to the use of general alcohols for precipitating plasmid DNA. However, **the claims do not relate simply to <u>any</u> alcohol**. Rather, claim 17, which is dependent either directly or indirectly on claim 15, relates to a subset of alcohols, i.e., those which can precipitate the plasmid DNA from the butanol, and claim 15 is directed to a "precipitating agent." Moreover, independent claims 1, 13, 14, and 37 are directed to a step of "recovering the plasmid DNA from the butanol" **<u>without specifying any use of alcohol</u>**.

Claims 3-7, 9-12, 16, 19-23, and 38-40 are dependent, either directly or indirectly, on claim 1 or claim 37, and the same arguments also apply to those claims.

For these reasons, while Applicants respectfully traverse the Examiner's rejection of claims 1, 3-7, 9-23, 25-26, 37-40, and 45-46 under 35 U.S.C. § 112, first paragraph, Applicants respectfully assert that the claims are in a condition for allowance.

Therefore, Applicants request reconsideration and withdrawal of the rejections made under 35 U.S.C. §112, first paragraph.

VII. Rejection of Claims 24-25, 29-33, 41-42, and 45 under 35 U.S.C. §102(e) is Traversed, but Partly Accommodated

The Examiner has rejected claims 24-25, 29-33, 41-42, and 45 under 35 U.S.C. §102(e) as anticipated by Colpan et al. (U.S. Pat. 6,383,393; entire document). This is a new rejection. Applicants respectfully traverse this rejection.

The Patent Office alleges:

> Colpan et al teaches methods for the purification of nucleic acids such as the isolation of plasmid of cosmid DNA from *E. coli* using an aqueous solution (column 2, line 1-10 and line 63-67). For the extraction of the DNA, the aqueous solution comprises high concentrations of chaotropic salts used in combination with aliphatic alcohols with a chain length of 1 to 5 carbon atoms (see e.g. column 4, line 66 through column 5, line 5). Specifically recited for use in the aqueous chaotropic solution is butanol (see e.g. column 5, line 20-27). Water is a weak base and is an essential element of the extraction mixture taught by Colpan et al. [P. 9.]

Applicants respectfully disagree, but have amended claims 24-25 and 30-31.

The present invention provides an extraction mixture which can selectively extract plasmid DNA from total DNA. The mixture contains both a chaotrope and an organic solvent (butanol). **The organic solvent is immiscible with the chaotrope-containing aqueous phase.** In use, the plasmid DNA migrates to the organic layer (i.e., the organic solvent phase) and the genomic DNA remains in the aqueous layer. The plasmid DNA can then be recovered from the organic phase. Claims 24-25 and 30-31 have been amended to emphasize this point. Claims 29, 32-33, 41-42, and 45 are dependent, either directly or indirectly, on one of these independent claims, and the same reasoning applies to them.

In contrast, **Colpan does not disclose a biphasic extraction mixture** of organic solvent, chaotrope and water. Colpan discloses methods for the purification of nucleic acid fragments and "**an aqueous solution** that can be used in the methods of the invention" (col. 2,

ll. 9-10). This aqueous solution is used to ensure that nucleic acids are quantitatively fixed onto the surface of a mineral substrate material. In column 5, lines 25-29, as quoted above, Colpan clearly states that the **butanol is present in the aqueous adsorption solution.** At the lines cited by the Patent Office with respect to the use of butanol in the aqueous chaotropic solution, Colpan states, in pertinent part:

> The lower alcohols present in the solution of the chaotropic salts are methanol, ethanol, isopropanol, butanol, and pentanol in amounts of 1 to 50%, **inasmuch as they are miscible with water within these ranges.** [Col. 5, ll. 25-29; emphasis added.]

Therefore, Colpan teaches that the alcohol must be miscible with the chaotrope-containing aqueous solution.

For these reasons, Applicants respectfully traverse the rejection of claims 24-25, 29-33, 41-42, and 45 under 35 U.S.C. §102(e) and respectfully submit that the claims are in a condition for allowance.

Therefore, Applicants request reconsideration and withdrawal of the rejections made under 35 U.S.C. §102(e).

VIII. Rejection of Claim 28 Under 35 U.S.C. §103(a) is Traversed

The Examiner has rejected claim 28 under 35 U.S.C. §103(a) as obvious over Colpan et al. (U.S. Pat. 6,383,393; entire document) in view of Sawadogo and Dyke (NAR, 19(3): 674 (1991); entire document). This is a new rejection. Applicants traverse this rejection.

The Patent Office alleges:

> Applicants claim an extraction mixture which comprises butanol, a chaotrope, and water. Butanol is n-butanol, 2-methylproponal or butan-2-ol.

> The teachings of Colpan et al are described above and are applied as before except; Colpan et al do no teach that Butanol is n-butanol, 2-methylproponal or butan-2-ol.
>
> Sawadogo and Dyke teach the use of n-butanol in the extraction of oligonucleotides (see e.g. column 1, paragraph 3).
>
> It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the butanol taught by Colpan et al with the n-butanol taught by Sawadogo and Dyke because Colpan et al teach that it is within the ordinary skill of the art to use butanol in an extraction mixture and because Sawadogo and Dyke teach that it is within the ordinary skill of the art to use n-butanol for extraction of DNA. One would have been motivated to do so in order to receive the expected benefit of reduced organic contaminants following use of n-butanol (Sawadogo and Dyke, page 674, column 1, paragraph 3). Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention. [P. 10.]

Applicants arguments with respect to Colpan have been outlined above and apply here as well. Colpan teaches that the alcohol must be miscible with the chaotrope-containing aqueous solution. Therefore, it is irrelevant whether Sawadogo and Dyke teaches that n-butanol can be used in the extraction of oligonucleotides. The skilled person would not have been motivated by Colpan to use n-butanol in a biphasic extraction solution and would not have arrived at the present invention.

IX. Objection to Claims 27, 34-35, 43-44, and 47 is Acknowledged

The Examiner has objected to claims 27, 34-35, 43-44, and 47 as being dependent upon a rejected base claim, but allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Applicants thank the Examiner for this acknowledgement, but have decided to await further prosecution of the base claims before proceeding with the objected claims, if possible.

X. Conclusion

It is believed that all outstanding rejections have been addressed by this submission and that all the claims are in condition for allowance. If discussion of any amendment or remark made herein would advance this important case to allowance, the Examiner is invited to call the undersigned as soon as convenient.

In view of the foregoing amendments and remarks, the present application is respectfully considered in condition for allowance. An early reconsideration and notice of allowance are earnestly solicited.

Applicants hereby request a three-month extension of time for the Amendment and accompanying materials. If, however, a petition for an extension of time is required, then the Examiner is requested to treat this as a conditional petition for an extension of time and the Commissioner is hereby authorized to charge our deposit account no. 04-1105 for the appropriate fee. Although it is not believed that any additional fee (in addition to the fee concurrently submitted) is required to consider this submission, the Commissioner is hereby authorized to charge our deposit account no. 04-1105 should any fee be deemed necessary.

Respectfully submitted,

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